REMARKS

This amendment is responsive to the final Office Action mailed July 16, 2003. There is only one grounds for rejection maintained against the present application, namely, lack of enablement under 35 U.S.C. §112, first paragraph. The central issue is thus, whether Applicant's specification provides a sufficient description to enable persons skilled in the art to practice the methods of treatment as they are defined in the claims. Because the invention *as set forth in the amended claims herein* is clearly enabled by the teachings of the specification coupled with the level of skill of the practitioners in the art, Applicant requests reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, and allowance of the application.

Applicant herein requests entry of an amendment to independent Claim 31. Specifically, Applicant requests amending the preamble of Claim 31 to recite: " a method of inhibiting the development and progression of atherosclerotic lesions in a human or other animal in need of treatment thereof ". Support for the amendment is found in Example III on pages 22-27, and in particular, page 22, lines 29-39, and page 27, lines 10-13. Since this requested amendment is in response to a rejection of the claims under 35 U.S.C. §112, first paragraph as overbroad, Applicant believes the amendment falls within the definition of amendments "complying with any requirements of form expressly set forth in a previous Office action" as set forth in 37 C.F.R. §1.116. Additionally, since the amendment more clearly and particularly points out that which Applicant regards as his invention, Applicant requests entry of the amendment as "presenting rejected claims in better form for consideration on appeal", also as set forth in 37 C.F.R. §1.116.

Summary of the Office Action

Applicant notes that the final Office Action mailed July 16, 2003 is substantially a verbatim repeat of the Office Action mailed November 12, 2002, with the exception that the Examiner now considers independent Claims 17, 22, and 27 to be enabled, if they were to be limited to an intradermal or intramuscular route of administration. For example, on page 2 of the Office Action, the Examiner states:

> "Claims 17-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for
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> The method as recited in any of the base claims 17, 22 and 27, wherein the route of administration of the claimed DNA vaccine is limited to intradermal administration or intramuscular administration, does not reasonably provide enablement for a treatment and/or prevention of any cardiovascular disease in any human or animal as set

forth in claim 31, and for any other route of administration that must exhibit a vaccine effect in any human or large animal or mammal."

As noted above, Claim 31 would still be considered overbroad *even if* limited to the specific routes of administration above, because the Examiner considers the totality of the art to question whether CETP activity in fact contributes to cardiovascular disease. (See, e.g., the Examiner's comments on page 12, line 15; page 15, line 14; page 16, line 19; page 19, line 1; and page 20, line 11, of the Office Action.)

Response to issues presented under 35 U.S.C. §112, first paragraph

Claims 17-35 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. Specifically, the Examiner breaks the enablement issue into two separate groups:

I. Independent Claims 17, 22, and 27, are considered overbroad as to means of *administration* of the DNA plasmid-based vaccines; and

II. Claim 31 is objected to as overbroad because of the *scope of the preamble*, which recites a method of *treating cardiovascular disease*.

Applicant traverses the rejections for the reasons set forth below.

I. Means of administering the DNA plasmid-based vaccines of Claims 17, 22, and 27

Claims 17, 22, and 27 recite methods of elevating the ratio of circulating HDL to circulating LDL, VLDL, or total cholesterol, methods of decreasing the level of endogenous CETP activity, and methods for eliciting production of anti-CETP antibodies, respectively. All of the above methods are accomplished by the administration of DNA plasmid-based vaccines that comprise a plasmid DNA molecule containing a DNA sequence encoding an immunogenic fusion polypeptide having at least one helper T cell epitope portion and at least one B cell epitope portion comprising a B cell epitope of CETP. When administered to a human or animal subject, the DNA plasmid-based vaccine, upon expression of the immunogenic fusion protein, will induce the production of autoantibodies specifically reactive *not only* against the fusion protein immunogen *but also* reactive with the individual's endogenous CETP. These antibodies inhibit endogenous CETP activity or remove CETP from circulation (clearance),

promote the formation and maintenance of an anti-atherogenic serum lipoprotein profile (for example, increased HDL levels and decreased LDL levels), and/or inhibit the development of atherosclerotic lesions.

While the Examiner considers these claims to be enabled if limited to intradermal and/or intramuscular administration (*see*, Office Action, page 2), the Examiner expresses his belief that other known means of administering plasmid-based vaccines are not enabled:

> "[T]he lack of reasonable correlation between intramuscular and/or intradermal injection and any other route of administration in large animals, as evidenced by McCluskie (DNA vaccine review articles), Anderson (DNA therapy review article) and Verma (DNA therapy review article), is indicative of the lack of reasonable enablement of the full breadth of the claimed invention." (Office Action, page 20, lines 2-6.)

Applicant respectfully traverses. The above references merely teach that the efficacy of DNA vaccines vary depending upon various routes of administration chosen. Variation, however, does not equate to non-enablement. It is well within the skill of the practitioner to make minor modifications based on the teachings of Applicant's specification to obtain a more efficacious result for the particular method of administration chosen by the practitioner. Applicant agrees that intramuscular and intradermal injection methods have been shown to be the most efficacious in clinical trial results to date, however they are not the only suitable ways of administering the DNA vaccines to achieve the desired result.

The Examiner points to McCluskie to show the lack of desirable efficacy of certain administration routes, for example, non-injected routes of administration. For instance, the Examiner cites the following McCluskie passage to support his contention that only intramuscular and intradermal routes of administration are enabled:

> "The generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, and antigens, and, unless the mucosal surface has been broken or damaged, transfection efficiency using naked DNA is low." (McCluskie, page 296, first column, lines 15-22.)

However, the McCluskie reference itself goes on to discuss additional means available to the skilled practitioner to increase the efficacy of the DNA vaccine *if such a noninjected route of administration is chosen by the practitioner:*

> "Efforts to circumvent this [lack of efficacy of non-injected routes of administration] have included formulation of the plasmid DNA with cationic lipids (24, 29, 32), the use of mucosal adjuvants (27, 28, 32), microencapsulation for oral delivery (30, 31, 66), or physical penetration of naked DNA into mucosal tissue using a GG (34, 36). (McCluskie, page 296, first column, lines 22-27.)

From the above it is apparent that a variety of additional means is available to the skilled practitioner to overcome that stated efficacy problems *should the skilled practitioner opt for a non-injected route of administration.* Applicant's claims cannot supplant and do not seek to supplant the wisdom and training of the practitioner in deciding which way to practice the invention, i.e., which route of administration to chose. The Applicant is only responsible for clearly describing how to put the methods of the invention into practice, not for pre-selecting the options available to any practitioner in this art. The relevant inquiry here is whether the practice of the invention is possible for the skilled person, given the information contained in the specification, combined with the common knowledge of persons skilled in the art. Applicant has provided sufficient information and exemplification to practice the invention in mammalian subjects and to obtain the desired results. Applicant has therefore satisfied the requirements of 35 U.S.C. §112, first paragraph, and no additional, non-statutory requirements should be held against the claims.

Applicant's note that the Verma and Anderson articles are primarily concerned with gene therapy, that is, preferential integration of the DNA into the human chromosome. **The present invention does not involve gene therapy.** Rather, the present invention involves the use of a DNA vaccine, calling for transient expression of an immunogenic vaccine peptide in tissues of a vaccinated host mammal, in order to produce an *in situ* immune response eliciting production of native antibodies capable of binding endogenous CETP of the host. Applicant's invention does not seek the production of transgenic subjects and does not require gene replacement in a subject. Therefore, the Examiner's comments on the complexity and unpredictability of methods of administering gene therapy vectors are regarded as irrelevant to the present invention.

Applicant points out that the mere fact that particular methods of administration of DNA vaccines have been shown to be more efficacious than others does equate to non-enablement of the less preferred methods of administration. Applicant expressly teaches, e.g., at page 8, last paragraph, and page 19, first paragraph, that the DNA plasmid-based vaccines of this invention "may be administered by any means normally used to administer plasmid-based vaccines to humans or animals." The methods of the

invention therefore should not be limited by particular mode of administration, selection of which is within the skill in the art and is not related to the inventiveness of the methods.

The breadth of the claims as written is fully enabled; accordingly, Applicant requests reconsideration and withdrawal of the rejection of Claims 17-35 under 35 U.S.C. §112, first paragraph.

II. Treatment According to Claim 31

The Examiner objects to Claim 31 as overbroad, stating:

> "On the basis of the totality of the art of record, the complexity of the nature of the invention, the lack of an art-recognized model for atherosclerosis, the doubts expressed in the art of record as to applicant's reliance on the inhibition of endogenous CETP circulated in an intended subject such as human for providing any and/or all cardiovascular benefit (see claim 31, *emphasis added*), a skilled artisan would not have recognized that the as-filed specification provides a reasonable enablement to the claimed invention within the context of DNA vaccine for treating any atherosclerosis in any animal or human, and that a skilled artisan would not have to engage [in] undue experimentation to reasonably extrapolate from applicant's disclosure to any therapeutic or prophylactic application of applicant's claimed invention in treating any animal or human so as to provide any cardiovascular benefit." (Office Action, page 12, second full paragraph down; see also page 15, line 14; page 16, line 19; page 19, line 1; and page 20, line 11.)

Applicant traverses the rejection; however, without acquiescing in any way to the reasoning of the rejection, but in an effort to advance prosecution, applicant has amended Claim 31 herein to recite:

> "A method of ~~treating cardiovascular disease~~ inhibiting the development and progression of atherosclerotic lesions in a human or other animal in need of treatment thereof comprising administering to said human or other animal a DNA plasmid-based vaccine comprising a DNA segment comprising a nucleotide sequence coding for an immunogenic polypeptide, which nucleotide sequence includes at least one segment coding for a B cell epitope of CETP linked in-frame with at least one segment coding for a broad range helper T cell epitope, which nucleotide sequence is operably linked to a promoter sequence suitable for directing the transcription of the nucleotide sequence in a mammalian cell."

The Examiner acknowledges that Applicant has enabled a method of inhibiting the development and progression of atherosclerotic lesions (notwithstanding the route of administration concerns, addressed above). See page 16 of the Office Action, inset paragraph:

> "The application further states provides guidance and/or factual evidence showing a rabbit model for atherosclerosis, wherein an intramuscular injection of a plasmid-based vaccine expressing a CETP peptide elicits an increased immune response that effects a reduction in endogenous CETP, and a reduction of atherosclerotic lesions in rats [sic, rabbits] fed with cholesterol." (Emphasis in original.)

Accordingly, Applicant believes the amendment to Claim 31 has either overcome or rendered moot the remaining enablement concerns of the Examiner.

Applicant has already made of record his challenges to the Examiner's comments that there is a lack of an art-recognized atherosclerosis model, that there is any doubt in the art or after reading the present specification that inhibition of CETP activity provides a cardiovascular benefit, and that a person skilled in the art would have any difficulty performing the steps of the claimed methods and observing the results. See, for example, Response filed May 12, 2003, pages 7-12.

By following the descriptions and examples of the specification, a person skilled in the art can readily put the methods claimed into use without experimentation and can readily determine the effectiveness of those methods in raising an antibody response which controls native CETP activity, alters HDL levels, and achieves an anti-atherosclerotic lipoprotein profile. In view of this, it is submitted that the adequacy of the specification to enable the methods of the claims is clear, and the requirements of 35 U.S.C. §112, first paragraph, have been amply met.

Accordingly, for the reasons set forth above, reconsideration and withdrawal of the rejection of Claims 17-35 under 35 U.S.C. §112, first paragraph, are respectfully solicited.

Respectfully submitted,

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